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The Flow Thermolysis of Pseudoakuammigine

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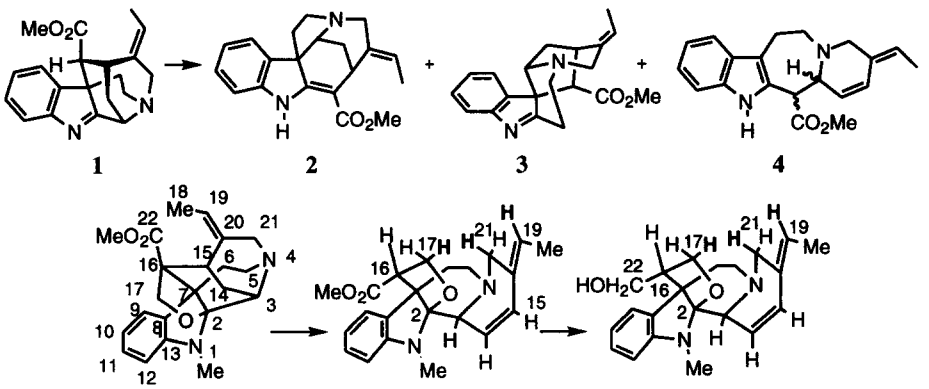
Abstract : Flow-thermolysis of pseudo-akuammigine (**5**) yielded 15,16-*seco*-14,15-dehydropseudo-akuammigine (**6**) with a *cis* C/D ring junction. © 1997 Elsevier Science Ltd.

We reported in previous papers[1] on the flow thermolysis of indole alkaloids in the *aspidosperma*, *strychnos*, and *akuamma* series. Most of the starting compounds were indolenines, and their rearrangement products were mainly the consequence of [1,5]-shifts, as for strictamine (**1**) rearranging[1c] to **2** and **3** (Scheme). However compound **4** with the ngouniensine skeleton resulted from an [1,3]-shift process.



Pseudoakuammigine **5**[2,3] is an indolinic alkaloid closely related to strictamine **1**, and it was of interest to study its possible thermal rearrangement(s). Flow thermolysis[1] of **5** (MeOH/toluene 8:2, 485±5°C, 15-20 mm Hg) yielded the isomeric (MS) compound **6**[4] (20%, rec). Compound **6** had retained the aminal group present in **5**, as indicated by the ^{13}C signal of C-2 at 105.1 ppm, while HMBC/HMQC[5] and ^{1}H-^{1}H COSY experiments evidenced the now tertiary C-16 and its relationship with the C-17 H_2. The NMR experiments also established the formation of the dienic system C-14 = C-15 - C-20 = C-19. Upon reduction with $LiAlH_4$ (THF, reflux, 1h), **6** yielded alcohol **7**[6] (76%), in which the aminal group was unaffected (C-2 resonating at 106.6 ppm). COSY experiments further clearly established that the C-16 - C-22 bond had been retained in **7**, and therefore in **6**. Thus, the thermal rearrangement of **5** into **6** results from the cleavage of the 15,16-bond and from a [1,3] H-shift from C-14 to C-16. That the migrating hydrogen had pushed the methoxycarbonyl group in **6** in close proximity to the aromatic ring was indicated by the ^{1}H NMR signal of the OMe at 3.41

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pppm, and by NOE effects (Table 1) between H-16 and H-6. The mass spectra, the ^{1}H and ^{13}C NMR spectra of **6**[4] and **7**[6] and the HMBC correlations (Table 2) were in full agreement with the depicted structures. Moreover, small NOE effects between H-17 and H-19 for **6** and **7**, and between H-17 and H-21 for **7** (Table 2) implied that the molecules had somewhat retained the initial conformation of **5** with a *cis* junction of the two six-membered rings that share the basic nitrogen.[7]

Table 1. NOE effects %

H(a)-H(b)	**6**	**7**
(3) - (5)	*3.3*	*3.8*
(5) - (21)	*3.9*	*3.1*
(6) - (9)	-	*1.4*
(6) - (16)	*6.7*	*2.2*
(9) - (16)	-	*1.2*
(15) - (18)	-	*8.0*
(17) - (19)	*2.0*	*1.7*
(17) - (21)	-	*0.7*
(19) - (21)	*3.9*	*9.0*

Table 2. HMBC correlations

	6	**7**
H	C	C
3	15 ----------	14, 15
5	3, 6, 7, 21------	3, 6, 7, 21
6	2, 5, 7, 8, 16 --	2, 5, 7, 8, 16
14	3, 20 ----------	3, 20
15	3, 21 ----------	3, 19, 20, 21
16	6, 7, 8, 17, 22 -	6, 7, 8, 17, 22
17	2, 7, 16, 22 ----	2, 7, 16, 22
21	3, 5, 15, 19, 20	3, 5, 15, 19, 20
22	----------	7, 16, 17

No such allylic fragmentation of the 15,16 bond was encountered until now in the *akuamma* series.

References and Notes

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3. Biogenetic numbering after Le Men, J.; Taylor, W.I., *Experientia*, **1965**, *21*, 508-511.
4. Compound **6** (oil): $[\alpha]_D$ - 29.6 (c=0.2, MeOH); UV, 206, 232, 303 nm; IR (film), 3052, 2947, 2890, 2816, 2751, 1738, 1606, 1491 cm^{-1}; ^{1}HNMR ($CDCl_3$), 1.71 (d,3H, J=6.8, 18-H_3), 2.33 (m, 3H, 6-H_2,5-H), 2.80 (m, 1H, 5-H), 2.93 (s, 3H, NCH_3), 3.10 (dt, 1H, J=3.0, 12.8, 21-H), 3.24 (dd, 1H, J=8.3, 9, 16-H), 3.30 (m, 2H, 21-H,3-H), 3.41 (s, 3H, CO_2Me), 4.03 (dd, 1H, J=8.3; 9, 17-H), 4.26 (t, 1H, J=8.3, 17-H), 5.29 (q, 1H, J=6.8, 19-H), 6.09 (bd, 1H, J=10.5, 14-H), 6.37 (d, 1H, J=7.5, 12-H), 6.62 (m, 2H, 10-H, 15-H), 6.91 (dd, 1H, J=1.5, 7.5, 9-H), 7.13 (td, 1H, J=1.5; 7.5, 11-H); ^{13}C NMR ($CDCl_3$), 12.42(18), 28.53 (NCH_3), 32.90(6), 49.65(5), 51.44(CO_2Me), 55.77(16), 57.13(7), 58.89(21), 64.05(3), 68.42(17), 105.10(2), 105.85(12), 116.97(10), 120.93(19), 123;18(9), 123.76(15), 126.16(14), 127.66(8) 129.31(11), 130.61(20), 150.16(13), 170.67(C=O); MS, *m/z* 366, 335, 280, 263, 174, 134, 121; HRMS, obs. 366.1948, calc. for $C_{22}H_{26}N_2O_3$: 366.1943.
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6. Compound **7** (foam): $[\alpha]_D$ -90.2 (c=0.6, MeOH); UV, 208, 236, 304 nm; ^{1}H NMR ($CDCl_3$) 1.70 (d, 3H, J=6.8, 18-H_3), 2.09 (ddd, 1H, J=3.0, 9.8, 12.0, 6-H), 2.25 (td, 1H, J=2.3; 11.3, 5-H), 2.35(m, 1H, 6-H) 2.43 (m, 1H, 16-H), 2.70 (dt, 1H, J=3.8; 11.3,5-H), 2.99 (s, 3H, NCH_3), 3.03 (dt, 1H, J=12.3; 2.3, 21-H), 3.15 (m, 2H, 3-H, 22-H),3.30 (m, 2H, 21-H, 22-H), 3.55 (t,1H, J=8.3, 17-H), 4.37 (t, 1H, J=8.3, 17-H), 5.27 (q, 1H, J=6.8, 19-H), 6.12 (bd, 1H, J=9.8, 14-H), 6.36 (d, 1H, J=7.5, 12-H), 6.58 (dd, 1H, J=9.8; 2.6, 15-H), 6.70 (td, 1H, J=6.8, 1.1, 10-H), 7.05 (dd, 1H, J=6.8, 1.1, 9-H), 7.16 (td, 1H, J=6.8; 1.1, 11-H), 3.10-3.30 (1H, 22-OH); ^{13}C NMR ($CDCl_3$), 12.38(18), 28.45(NCH_3), 33.30(6), 50.33(5), 53.00(16), 55.16(7), 59.14(21), 63.05 (22), 64.23(3), 70.90(17), 105.71(12), 106.60(2), 117.35(10), 120.69(19), 122.96(9), 123.62(15), 126.62(14), 128.47(8), 129.05(11), 130.90(20), 149.85(13); MS,*m/z*: 338, 280, 279, 174, 167, 158, 149, 144, 134, 121; HRMS, obs.,338.1978; calc.for $C_{21}H_{26}N_2O_2$, 338.1994.
7. Molecular modelling calculations using SYBYL 6.03 package (TRIPOS), then AM1 (MOPAC) were kindly performed by Pr J.-C. Gramain and Dr D. Vallée-Goyer, whom we thank, showing that the *cis* structure **6** is more stable than the *trans* one by 8.6 kcal mol^{-1}.

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